The opinion in support of the decision being entered today is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
PAUL DAVID CANNON and SURYANARAYANA SANKURATRI

Appeal 2007-1139
Application 10/052,664
Technology Center 1600

Decided: September 20, 2007

Before TONI R. SCHEINER, DONALD E. ADAMS, and LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claim 1, which is reproduced below. We have jurisdiction under 35 U.S.C. § 6(b).

1. An isolated Npt2B polypeptide comprising the amino acid sequence set forth in SEQ ID NO:1.

The Examiner relies on the following references:

Peer Bork et al., "Predicting functions from protein sequences-where are the bottlenecks?" 18 *Nature Genetics*, 313-318 (1998).

Peer Bork et al., "Sequences and topology-Deriving biological knowledge from genomic sequences" 8 *Current Opinion in Structural Biology*, 331-332 (1998).

Karp "Editorial-What We Do Not Know About Sequence Analysis and Sequence Databases" 14(9) *Bioinformatics*, 753-754 (1998).

We reverse.

BACKGROUND

According to the Specification,

> Phosphorous plays an important role in membrane structure, transport and energy storage. At normal physiological pH (e.g. pH of 7.4), inorganic phosphate (Pi) in plasma is made up of a 4: 1 mixture of HPO_4^{2-} and H_2PO4^-. Of the 700 g of phosphorous present in the body, 0.1 % is present in the extracellular fluid in a freely diffusible form. The plasma level of Pi is maintained through control of Pi absorption in the small intestine, under the influence of vitamin D, and Pi excretion in the kidney, under the influence of parathyroid hormone.
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> Absorption of Pi requires transepithelial transport. A critical step of transepithelial transport of Pi is the uptake of Pi into epithelial cells. Pi uptake is accomplished by sodium phosphate co-transporters present on the apical surface of appropriate epithelial cells, e.g. intestinal and renal epithelial cells. A variety of sodium phosphate co-transporters have been identified to date, including: NaPi-1 (rabbit); NPTl (human); Npt 1 (mouse); NaPi-2 (rat); NaPi-3 (human); NaPi-4 (opossum); NaPi-5 (flounder); NaPi-6 (rabbit); NaPi-7 (mouse); and NaPi of NBL-1 cells (bovine).

> A variety of disease conditions are associated with disorders in Pi metabolism, where such disease conditions include those characterized by the presence of hypophosphatemia, e.g. osteomalacia, hypocalciuria and rickets, and those characterized by the presence of hyperphosphatemia, e.g. hyperparathyroidism, hypocalcemia, vitamin D deficiency, soft tissue or metastatic calcification, and the like. In particular, hyperphosphatemia is a characteristic of renal disease and failure, and is an underlying cause of many of the deleterious symptoms observed with such renal complications.

(Specification[1] 1-2.)

The invention is drawn to a novel human intestinal sodium phosphate co-transporter (Npt2B) polypeptide (*id.* at 3), and methods of treating disease conditions associated with Npt2B function, that is, conditions resulting in abnormal serum phosphate levels, such as hypo- and hyperphosphatemia (*id.*). The Specification discloses that "[i]n its native environment, Npt2B is a co-transporter of sodium cation and phosphate anion. Npt2B is expressed, among other locations, on the surface of intestinal epithelial cells, i.e. on the apical or intestinal luminal side of the epithelial cells, and therefore provides for the transport of sodium and phosphate ions from the intestinal lumen into the intestinal epithelial cells." (*Id.* at 4.)

Based on sequence homology, the Specification discloses that the claimed Npt2B polypeptide, which is expressed in human small intestine, appears to be a member of the bovine/flounder type II contransporter subfamily (*id.* at 28-29). The Specification also discloses cloning the

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[1] All references to the Specification are to the Substitute Specification, dated May 10, 2002.

polypeptide into mammalian cells, and teaches methods of assaying for Na/Pi transporter activity (*id.* at 29-30).

The Specification teaches further that antibodies that bind to Npt2B may be used to reduce or inhibit Npt2B activity in a host, and thus limit or stop Pi transport, and thus reduce plasma Pi levels (*id.* at 19-21, 25). According to the Specification, "[d]isease conditions resulting from abnormally high Npt2B activity are those characterized by the presence of hyperphosphatemia and include: hyperparathyroidism, hypocalcemia, vitamin D deficiency, soft tissue or metastatic calcification, and the like. Of particular interest is the use of the subject methods to treat hyperphosphatemia resulting from renal insufficiency, e.g. caused by renal disease resulting in at least impaired renal functions, and the like." (*Id.* at 27.)

DISCUSSION

UTILITY

Claim 1 stands rejected under 35 U.S.C. § 101 on the grounds that the claimed invention is not supported by either a specific and substantial utility or a well-established utility.

The Examiner notes that the Specification discloses that the Npt2B polypeptide of SEQ ID NO:1 is a human intestinal sodium phosphate co-transporter, and that the Specification also discloses disorders in inorganic phosphate (Pi) metabolism and that methods of treating such disorders are varied (Answer 4).

The Examiner asserts, however, that "[m]embers of the sodium phosphate co-transporter family are highly divergent in their effects and ligand specificity." (*Id.*) Moreover, according to the Examiner, "[t]here is

no experimental data provided as to the specific functionality of the claimed Npt2B," nor is there a "disclosure of the specific ligands that activate or bind it." (*Id.*) Because there is no disclosure as to the specific ligands, the Examiner concludes that the claimed polypeptide is an "orphan receptor," and thus there is no utility for a ligand having no known function that binds to an Npt2B of no known function (*Id.* at 6). Thus, the Examiner asserts, "[t]he inclusion in the family of sodium phosphate co-transporters does not constitute either a specific and substantial asserted utility or a well-established utility for the claimed Npt2Br protein." (*Id.*)

The Examiner argues that while the Specification teaches that the claimed Npt2B polypeptide is useful for applications such as research, diagnostic and therapeutic agent screening applications, and methods of treatment, "[t]here is no clear nexus between any treatable diseases/disorders and use of the claimed Npt2B," and "[t]here is no disclosure of the specific activity of the claimed sodium phosphate co-transporter or how to assay for said activity." (*Id.* at 4-5.)

Appellants argue that "the Examiner has not met the burden of presenting a *prima facie* case that the claimed invention lacks patentable utility because he a) failed to provide any evidence or factual reasons why one skilled in the art would reasonably doubt the asserted utilities of the claimed Npt2B polypeptide and b) misinterpreted the facts in the filed of the art and concerning factual statements contained in the specification." (Br.[2] 6.)

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[2] All references to the Brief (Br.) are to the Appeal Brief dated September 28, 2005.

The Examiner bears the initial burden of showing that a claimed invention lacks patentable utility. *See In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.").

The Court of Appeals for the Federal Circuit addressed the utility requirement in *In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), as rejecting a "de minimis view of utility." 421 F.3d at 1370, 76 USPQ2d at 1229. The *Fisher* court held that § 101 requires a utility that is both substantial and specific. *Id.* at 1371, 76 USPQ2d at 1229. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." *Id.*, 76 USPQ2d at 1230.

The court held that a specific utility is "a use which is not so vague as to be meaningless." *Id.* In other words, "in addition to providing a 'substantial' utility, an asserted use must show that that the claimed invention can be used to provide a well-defined and particular benefit to the public." *Id.*

We agree with Appellants that the Examiner has not provided a sufficient basis to challenge the Specification's assertion of utility, and the rejection is reversed.

The Examiner asserts, relying on Bork (Nature Genetics), Karp, and Bork (Current Opinion in Structural Biology) that the "utility of the claimed protein cannot be implicated solely from the homology to the proteins known in the art because the art does not provide a teaching stating that all protein disclosed have the same activity, same effects, the same ligands and or are involved in the same disease states." (Answer 5.)

Bork (Nature Genetics), according to the Examiner, "provides a review disclosing the problems of using homology detection methods to assign function to related members of a family." (Answer 7.) Bork (Nature Genetics) is also cited by the Examiner for teaching that while the function of a protein may be identified using homology, the prediction of substrate specificity "is unwarranted." (*Id.* at 8) Karp and Bork (Current Opinion in Structural Biology) also discuss the problems of using analysis of sequence homology to predict function (*id.* at 8-9). The Examiner concludes that the references "disclose the unpredictability of assigning a function to a particular protein based on homology, especially one that belongs to the family sodium phosphate co-transporter which has very different ligand specificity and functions." (*Id.* at 9.)

First, the above references relate to the issues of assigning function using sequence homology generally, and are not specific to the family of sodium phosphate co-transporters. The references in fact support that it is not an absolute, *per se*, rule, that in every factual circumstance sequence homology cannot be used to predict function. Thus, the references do not

establish that the skilled artisan would find function based on sequence homology to be incredible.

As also noted by Appellants (Br. 8), the Specification teaches that Npt2B is a human type II sodium phosphate co-transporter that provides for the transport of sodium and phosphate ions from the intestinal lumen into the intestinal epithelial cells, and does not require another ligand for activity. Appellants rely on the Declaration filed under 37 C.F.R. § 1.132 of Suryananrayana Sankurati (Declaration), dated February 18, 2004, which states at paragraph 3:

> Using the procedure that was disclosed in the application (page 29 line 25 to page 30 line 19), we were able to show that CHO cells which express the human Npt2B protein of this invention were able to transport phosphate ions as measured by the amount of radioactive phosphate taken up by the cells, whereas CHO cells not expressing Npt2B did not transport phosphate. This result, graphically represented in Fig. 1, clearly demonstrated that Npt2B is a phosphate transporter.

The Declaration also presents data demonstrating that the transporter requires the presence of sodium (see Figure 2 of the Declaration), and that "Km measurements for sodium and phosphate uptake for Npt2B were remarkably similar to those obtained from intact intestinal membrane vesicles (Declaration ¶4).

The Examiner dismisses the Declaration, stating that "[t]he inclusion in the family of sodium phosphate co-transporter does not constitute either a specific and substantial asserted utility or a well-established utility for the claimed Npt2B polypeptide," asserting that is "analogous to the reasoning that all proteins/nucleic acids of sodium phosphate co-transporter proteins can be used as markers on a gel." (Answer 22.) According to the Examiner,

"[a] utility for Npt2B cannot be assigned without knowledge of what disease is associated with Npt2B dysfunction or what drugs/ligands affect Npt2B function." (*Id.* at 22-23.)

We disagree. First, the Declaration followed the procedures set forth in the Specification and is used to substantiate the utility set forth in the Specification, and not to establish a utility. *See In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). The Specification clearly states that the Npt2B polypeptide is a co-transporter of sodium cation and phosphate anions and is expressed, among other locations, on the surface of intestinal epithelial cells, i.e. on the apical or intestinal luminal side of the epithelial cells, providing for the transport of sodium and phosphate ions from the intestinal lumen into the intestinal epithelial cells. The Specification also characterizes the polypeptide as a type II transporter. The Examiner has not brought forth any evidence or argument as to why one skilled in the art would not find credible the asserted function of the Npt2B polypeptide beyond relying on evidence that states that polypeptide function may not always be predicated on sequence homology.

As to the Examiner's assertion that a utility for Npt2B cannot be assigned without knowledge of what disease is associated with Npt2B dysfunction or what drugs/ligands affect Npt2B function, the Specification teaches that Npt2B is involved in the absorption of Pi from the intestine. As such, the reduction or inhibition of Npt2B activity in a host would limit or stop Pi transport, thus reducing plasma Pi levels. The Specification also sets forth disease states that are characterized by the presence of hyperphosphatemia where reduction in plasma Pi levels is desirable, which disease states include: hyperparathyroidism, hypocalcemia, vitamin D

deficiency, soft tissue or metastatic calcification, and the like, and of particular interest is the reduction in plasma Pi levels to treat hyperphosphatemia resulting from renal insufficiency, e.g. caused by renal disease resulting in at least impaired renal functions.

We also find that such a utility would be credible to the skilled artisan. Appellants rely on Peerce ("Inhibition of human intestinal brush border membrane vesicle Na+-dependent phosphate uptake by phosphophloretin derivatives," *Biochem. Biophys. Res. Comm.*, Vol. 301, pp. 8-12 (2003)) (Br. 13), which states at page 8 that "[a] pharmacological method of reducing intestinal phosphate absorption may provide a more palatable approach to reducing serum phosphate and may slow the progression of moderate chronic renal failure to end-stage renal failure." Even though Peerce was published after the filing date of the instant application, we find the quoted statement to be indicative of the state of the art at the time of filing. For Example, Feild (EP 0875569, published November 4, 1998, submitted in the IDS dated January 17, 2002), states that:

> Phosphate retention has been shown to play a critical role in the development of uremic bone disease. Blockade of intestinal absorption of phosphate could provide an important target for prevention of uremic bone disease in patients who have end stage renal disease (ESRD) and possibly a target for slowing the progression of the renal disease itself. Patients with ESRD cannot excrete phosphate, and they develop hyperphosphatemia, secondary hyperparathyroidism and uremic bone disease. Current treatment of these patients involves dietary phosphate restriction and phosphate binders, both of which have severe drawbacks. Blockade of phosphate absorption with a specific inhibitor of the intestinal phosphate transporter would provide a major advance in the treatment of these patients.

(*Id.* at 2.) Peerce and Feild thus establish that there was a known specific and substantial known utility for potassium sodium transporters that are involved in the absorption of Pi in the intestine.

In addition, as noted by Appellants (Br. 9), the Specification teaches that the Npt2B polypeptide may be used in the generation of antibodies that reduce or inhibit the function of Npt2B, which antibodies may be useful as therapeutics. Again, the Examiner has provided no evidence that one skilled in the art would not find such a utility credible.

The Examiner's primary concern appears to be that "[t]he claimed transporter was not expressed in intestinal cells or any other cells to determine its ion transport properties. *The functionality of claimed transporter is based solely on homology to other transporter polypeptides.*" (Answer 20 (emphasis added).) The Examiner's concern, therefore, seems to be that the disclosure as filed predicated utility and function on sequence homology. The USPTO has, however, rejected a *per se* rule as to homology.

> The suggestions to adopt a *per se* rule rejecting homology based assertions of utility are not adopted. An applicant is entitled to a patent to the subject matter claimed unless statutory requirements are not met (35 U.S.C. 101, 102, 103, 112). When the USPTO denies a patent, the Office must set forth at least a *prima facie* case as to why an applicant has not met the statutory requirements. The inquiries involved in assessing utility are fact dependent, and the determinations must be made on the basis of scientific evidence. Reliance on the commenters' *per se* rule, rather than a fact dependent inquiry, is impermissible because the commenters provide no scientific evidence that homology-based assertions of utility are inherently unbelievable or involve implausible scientific principles. *See, e.g., In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (rejection of claims improper where claims did "not suggest an inherently

> unbelievable undertaking or involve implausible scientific principles' and where ''prior art * * * discloses structurally similar compounds to those claimed by the applicants which have been proven * * * to be effective'').
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> A patent examiner must accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The examiner's decision must be supported by a preponderance of all the evidence of record. *In re Oetiker,*977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. ''[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient.'' *Fujikawa v. Wattanasin,* 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996). The Office will take into account both the nature and degree of the homology.

Utility Examination Guidelines, 66 Fed. Reg. 1092, 1096 (USPTO January 5, 2001).

In the case before us, Appellants disclosed in the Specification that the claimed Ntp2B polypeptide is a type II potassium sodium co-transporter. Appellants then filed a Declaration which, using the procedures disclosed in the Specification, substantiated that utility. The Examiner has failed to establish by evidence or sound reasoning that the utilities in the Specification would not be credible to the skilled artisan for the reasons set forth above, and the rejection must be reversed.

ENABLEMENT

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, because, "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility . . . , one skilled in the art clearly would not know how to use the claimed invention." (Answer 15.) Because we are reversing the utility rejection, we also reverse the enablement rejection of claim 1.

CONCLUSION

In summary, as the Examiner has failed to establish that the polypeptide of claim 1 lacks a patentable utility, we reverse.

REVERSED

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ROCHE PALO ALTO LLC
PATENT LAW DEPARTMENT M/S A2-250
3431 HILLVIEW AVENUE
PALO ALTO, CA 94304